STATISTICAL ANALYSIS PLAN
SU017 STUDY – ALTIS
FINAL ANALYSIS - 2022

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Table des matières

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1. MAIN OBJECTIVES OF STUDY AND STATISTICAL ANALYSIS:

Coloplast's Altis Single Incision Sling (SLIS) System is a minimally invasive system intended for the treatment of female stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency in women.

To meet the requirements of the AFNOR standard, an observational study has been organized to prospectively collect short and mid-term data in the treatment of the female SUI with Altis SIS in the real world. Indeed, observational studies are essential to understand real world use and compliance patterns, estimate effectiveness, and to adequately evaluate risk management programs.

The primary objective is assessment of clinical effectiveness defined by success that is a composite criterion including the patient global impression of improvement (PGI; very much better, much better, little better) and the absence of serious/severe related adverse event (AE), one year after implantation definition.

The secondary objectives of the study are:

- Clinical effectiveness of Altis SIS over the 3 years of follow-up
- Comparison between pre and post inclusion for other outcomes:

  Objective: cough stress test, uro-flowmetry exams: post-void residual volume and peak urine flow rate, weights of urinary protection.

  Subjective: number of pads used, exploration of impact of Altis SIS on quality of life via PGI-I, I-QOL or ICIQ-UI-SF questionnaires, patient's satisfaction, and exploration of impact of Altis SIS on sexual life via PISQ-12 questionnaire.
- Documentation of emergent device-related A.E. and safety over the 3 years post implantation
- To explore the pre-surgery prognosis factors associated of treatment success.

2. SUMMARY OF STUDY DESIGN FEATURES:

2.1 Study design:

This study is a multicenter prospective, observational, post-market cohort study of women with urinary incontinence implanted with Altis Single Incision Sling System. Patients will be recruited by specialized surgeons who are trained to the implantation of Altis. They will be followed for 12 months in routine clinical practice. Data will be collected by questionnaires through an electronic

data capture system during routine visits occurring approximately at baseline, between 1 and 3 months (first follow-up visit) and 12 months. An annual follow-up, each year during 2 additional years will also be performed during a visit at the site or via postal questionnaire at surgeon's discretion or according to his current practice. The objective during these additional follow-ups is to obtain completed patient's self-questionnaires.

2.2 Sample size:

Effectiveness of female SUIs managed with sling implantation is not accurately defined and large range of success of the procedure is reported.

Furthermore, definition of success is not standardized and comparison across studies and systems is not feasible due to different used endpoint criteria.

Accordingly if p is the % of success as defined in this protocol, the product p*(1-p) should be maximized. According to the interim results of an US study, the PGI score at 1 year is 89.3 %.

So this hypothesis of a 89 % rate could be chosen. Therefore, the minimal sample size to be included to detect this prevalence with a 5 % precision is given as following:

$Sn= z^2p(1-p)/d^2$.

Precision (d) = 5 % prevalence (p)= 89 % estimated sample size n= 150

The total number of subjects enrolled is not limited. However, a minimum of 150 subjects with 12-month available data will be collected. Taking into account a global attrition rate of 20%, 180 patients are targeted for enrolment.

When 150 subjects will have reached a minimal 12-month follow-up duration and all cases are judged exploitable, Sponsor will take the decision to stop or to continue the current recruitment.

Consequently, the centers have been encouraged to keep on enrolling patients after the first 180 patients defining an open-ended recruitment. Approximatively 600 patients have been finally included.

2.3 Randomization: not applicable

As it is a non-interventional study, there is no randomization.

2.4 Study population:

This project involved 4 countries: France, Germany, Italy and Spain and surgeons used Altis in their current practice. Experience in Altis implantation may vary between investigators sites.

The study population will consist of patients meeting all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria are the following:

- Female gender
- At least 18 years of age
- Subject implanted with Altis Single Incision Sling System in the participating center, to manage urinary incontinence according to urologist's diagnosis
- Subject's having received written and oral information about study objectives and having accepted that anonymous data issued from his medical dossier will be used for research purposes and will be analyzed by using computer systems. According to national regulations, a written consent to participate may be required.

Exclusion criteria are the following:

- Subject who refuses to be included in the survey or that their medical data will be used for research purposes
- Indication for Altis Single Incision Sling System implantation is not for the treatment of female UI.
- Subject already enrolled in any investigational clinical trial of any treatment (drug or device).

Subject withdrawal:

Patients will be totally free to withdraw from the study at any time.

2.5 Study assessments:

Assessments were based on both physician and patient reported outcomes (PRO). These PRO can be obtained by validated self-questionnaires given at the medical center during a patient's visit or sent by mail.

2.6 Study product:

Altis Single Incision Sling (SIS) System is a CE-marked since 2012 and already marketed implantable device. All the patients included in this study had a surgery but a few of them have not been finally implanted with Altis (implantation failure) and another device may have been implanted (results from interim analysis).

3. VARIABLES TO BE SUBJECTED TO STATISTICAL ANALYSES:

3.1 At baseline:

- *Subject' s demographics &Medical History:*
  - Age (+ sub groups: <65 and ≥ 65 year-old)
  - BMI (+ sub groups: lower-normal/over/obesity) (< 25/ 25-29,99 / ≥30)
  - Lifestyle (active, sedentary)
  - Smoking status
  - Comordities/medical/surgery/uro-gynecological history including Pelvic organ prolapse / hysterectomy / SUI
  - Menopausal status
  - Category of urinary incontinence (SUI, MUI, UUI, other UI)
  - Duration and cause of stress component (+ subgroups: < 5 years and ≥ 5 years)
  - Previous treatments of UI (including combined antimuscarininics and mirabegron)
  - Preexisting symptoms (dyspareunia / urgency symptoms)

- *Physical examination:*
  - Clinical tests :
    - Cough stress test
    - Cervico-urethral mobility (Marshall/Bonney Test, Ulmsten Test, Q Tip/cotton swab Test, other)
    - POP-Q:
      - If POP by grade and localization (anterior vaginal wall, apical, posterior vaginal wall)
      - POP associations

- *Nb of pads used/day (and by number of pads)*

- *Pad weight test (if done)*

- *Urodynamics testing (if done):*
  - maximum urine flow rate (+ Qmax < 15 ml)
  - post-void residual volume measurement (+ PVR > 150 ml)
  - Cystometry:
    - normal
    - bladder outlet obstruction,
    - detrusor over or underactivity,
    - urodynamic SUI
  - Measures of urethral pressure: (one of following methods)
    - MUCP
    - VLPP

- ALPP

- *Questionnaire ICIQ –UI-SF*
    - Sum items 3+4+5
    - Items 6

- *Questionnaire I-QOL:*
    - total scores and subscale scores: Avoidance and Limiting Behavior (ALB), Psychosocial Impacts (PS), and Social Embarrassment (SE).
    - demographic questionnaire

- *Questionnaire PISQ 12:*
    - total scores
    - Q5, Q6 and Q7 separately

3.2 Operative procedure:

- *Surgical Procedure* :
    - Type of anesthesia
    - Pre and intra-operative antibiotics
    - Concomitant pelvic surgery (type): hysterectomy and/or surgical cure of a pelvic organ prolapse, association, other
    - Blood loss
    - Intra-op complications
    - Duration
    - Technical observations

- *Immediate post-operative data:*
    - Post –operative antibiotics and duration
    - Spontaneous post-op micturition or urinary drainage and duration
    - Postoperative hospital stay/duration
    - Post-void residual volume at discharge
    - Maximum flow rate at discharge (if done)

3.3 follow up visits from first postoperative visit until 3 years after implantation:

- *Incision healing* (first post-operative visit only)
- *Local pain* (first post-operative visit only)
- *Physical examination / interview patient:*
    - Weight, BMI and change of BMI since baseline (excepted at first post-operative

visit)
- Urinary symptoms
- Nb of pads used (question from the investigator to the patient).
- Cough stress test

- Pad weight test (if done, according to current practice)

- *PVR and uroflowmetry (if available):*
  - post-void residual volume measurement
  - maximum urinary flow rate

- New Vaginal/Pelvic Intervention (confirmed by the investigator), excepted at first post-operative visit

- Questionnaire PGI-I

- Questionnaire ICIQ –Ui-SF
  - Sum items 3+4+5
  - Items 6

- Questionnaire I-QOL:
  - total scores and subscale scores

- Questionnaire PISQ -12:
  - total scores
  - Q5, Q6 and Q7

- Work stoppage: if yes, number of days (first follow-up visit only).

- Normal activity: number of days before returning to a normal activity (first follow-up visit only).

- Patient satisfaction

- Patient recommendation: recommend the surgery to a friend?

ICIQ-UI Short Form scoring: The ICIQ-UI Short Form is a questionnaire for evaluating the frequency, severity and impact on quality of life (QoL) of urinary incontinence in men and women in research and clinical practice across the world. Questions 3, 4 and 5 are summed to compute the total ICIQ SF score. This score may be divided into the following four severity categories: slight (1-5), moderate (6-12), severe (13-18) and very severe (19-21).

i-QOL scoring: The I-QOL produces quality-of-life profiles for people suffering from urinary incontinence. The surveys consists of 22 items scored on a 5 -point Likert scale providing a transformed summary score of 0 to 100 with higher scores indicating better quality of life. The 22 items can be further grouped into 3 subscales: Avoidance and Limiting Behavior (8 items), Psychosocial Impacts (9 items), and Social Embarrassment (5 items). The I-QOL and its subscale scores are computed by adding each item's response, subtracting the lowest possible score and dividing that sum by the possible raw score range. The scores are then transformed to have a range from 0 (maximum problem) to 100 (no problem at all). The formula used to compute the transformed score follows:

Scale score= (sum of items-lowest possible score – lowest possible score) / possible raw score range*100
Missing data: if no more than three (of the 22) items are omitted, a mean substitution may be computed for these items. However it is recommended that i-QOL scores be set to missing if more than three items are left unanswered.

PISQ-12 scoring: the PISQ is a 12-item questionnaire with items selected through review of the literature, expert opinion and review of non-validated or generic questionnaires. Responses are graded on a 5-point Likert scale from 'never' to 'always'. The PISQ-12 is a validated and reliable short form that evaluates sexual function in heterosexual women with urinary incontinence and/or pelvic organ prolapsed and predicts long-form scores.
Scores are calculated by totaling the scores for each question with 0= always, 4=never. Reverse scoring is used for items 1,2,3 and 4. The short form questionnaire can be used with up to two missing responses. To handle missing values the sum is calculated by multiplying the number of items by the mean of the answered items. If there are more than two missing responses, the short form no longer accurately predicts long form scores. To make scores comparable to long form scores multiply the total by 2.58. Furthermore, questions 5, 6 and 7 can be evaluated separately.

The Patient Global Impression of Improvement (PGI-I) is a transition scale that is a single question asking to rate their urinary tract condition after treatment, as compared with how it was prior to before beginning treatment on a scale from 1 (very much better) to 7 (very much worse).

In case of discordances between the questionnaires and physician assessments, only questionnaires will be considered (number of pads used).

3.4 Complications since implantation:

Type, seriousness, severity (intensity), relatedness (device alone; device and/or procedure), Clavien-Dindo classification, System Organ Classes, High Level Term according to MedDRA, treatment initiated and localization of pain concerning side effects occurred since implantation, date of event onset according to IUGA classification and chronicity will be described.
If a complication/adverse event is declared by a patient, a medical confirmation by the investigator or the Scientific Committee will be required to be considered.

3.5 Study exit/ Withdrawal:

Completion of the study as planned and primary reason in case of discontinuation will be described.

4. EFFICACY AND SAFETY VARIABLES:

During the intermediate analysis, a Scientific Committee (SC) consisting of 3 experts has been consulted for reviewing the Statistics Analysis Plan and adjudicating all the safety events.
This Scientific Committee recommended modifications on the definition of treatment success without PGI-I "Little better" response deemed not relevant, and that includes Clavien-Dindo grade > 3 which is more relevant than the "severe" criterium often misinterpreted by the investigators.
Consequently, the analyses will be performed as defined in the protocol and as recommended by Scientific Committee.

4.1 Primary endpoint:

<u>As defined in protocol:</u>

Treatment success defined by PGI as a little, much better and very better improved and absence of serious or severe related Adverse Event one year after implantation.

Table 1: Definition of treatment success

Patient Global Improvement (PGI-I)	Safety	
	No severe or serious related adverse event reported	At least one severe or serious adverse event reported
Very much better	success	failure
Much better	success	failure
Little better	Success	failure
No change	failure	failure
Little worse	failure	failure
Much worse	failure	failure
Very much worse	failure	failure

As recommended and defined by Scientific Committee /SC:

- Treatment success defined by PGI as much better and very better improved and absence of any serious neither severe nor ≥ grade 3 of Clavien-Dindo classification related Adverse Event one year after implantation.

4.2 Secondary endpoints:

As defined in protocol:

- ✓ Treatment success defined by PGI as a little, much better and very better improved and absence of serious or severe related Adverse Event at first follow-up visit, 2 years and 3 years after implantation.

- ✓ PGI as a little, much better and very better improved at first follow-up visit, 1 year, 2 years and 3 years after implantation.

As recommended and defined by Scientific Committee /SC:

- ✓ Treatment success defined by PGI as much better and very better improved and absence of any serious neither severe nor ≥ grade 3 of Clavien-Dindo classification related Adverse Event at first follow-up visit, 2 years and 3 years after implantation.

- ✓ PGI as much better and very better improved at first follow-up visit, 1 year, 2 years and 3 years after implantation.

- ✓ Treatment success defined by PGI as much better and very better improved, and absence of serious related Adverse Event at first follow-up visit, 1 year, 2 years and 3 years after implantation.

- ✓ Treatment success defined by PGI as much better and very better improved, and absence of ≥ Grade 3 Clavien-Dindo classification related Adverse Event at first follow-up visit, 1 year, 2 years and 3 years after implantation.

- ✓ PGI as much better and very better improved at first follow-up visit, 1 year, 2 years and 3 years after implantation.

Objective exams at baseline, first follow-up visit, one year, two years, three years after implantation:

- ✓ cough stress test,
- ✓ number of pads/day,
- ✓ post-void residual volume,
- ✓ maximum urinary flow rate,

Subjective exams at: baseline, first follow-up visit, 1 year, 2 years and 3 years after implantation:

- ✓ total I-QOL score and subscale scores (ALB/PSI/SE),
- ✓ Total PISQ-12 score, Q5 Q6 and Q7 PISQ-12,
- ✓ total ICIQ score,
- ✓ satisfaction (only at follow-up visit),
- ✓ recommendation to a friend (only at follow-up visit)
- ✓ activity (only at first follow-up visit)

4.3 Safety endpoints:

Type, seriousness, severity (as intensity), relatedness (device alone; device and/or procedure), Clavien-Dindo classification, SOC, High level term according to MedDRA, revisions and treatments needed and localization of pain concerning side effects occurred since implantation.

5. DISPOSITION OF SUBJECTS:

The eligible population will include all patients who gave their informed consent and met the eligibility criteria. Patients who withdraw study before procedure (screening failure) won't be included in this population, as well as those who don't respect the inclusion criteria.
The ITT population will include all patients for whom a procedure has been performed even if the Altis sling has not been implanted (i.e Altis implantation failure and implantation of other device or none) among the eligible population excluding major deviation (GCP compliance), patient with no information at baseline, or patients implanted but not procedure form in eCRF.
All analyses will be performed on this population.

Last procedure happened in September 2020. As extraction of data is planned in July 2022, a few patients (20 approximatively) won't be able to complete the follow-up and/or the self-questionnaires at 3 years. Nevertheless, they should have theoretically completed their questionnaire at one year corresponding to the primary outcome; the data not completed at three years will be coded in a specific way to distinguish them to true missing values.

All visits for all patients included, whom data have been collected will be analyzed (baseline, first follow-up visit, 1 year, 2 years and 3 years after implantation). So, the final report will present longitudinal data and evolution over time of the different parameters (exams).
If any follow up visit is available, only patient's characteristics will be presented.

6. HANDLING OF PROTOCOL VIOLATIONS: not applicable

As this study is observational, there is no protocol violations.

7. HANDLING OF MISSING VALUES:

Missing data will remain missing in all endpoint derivations except for I-QOL and PISQ-12 questionnaires for whom specific guidelines will be applied. All summary tables will be based on data without imputation of missing values.
For multivariate logistic regression (study of factors associated to success of treatment), if missing values concern most of the covariates, multiple imputation may be needed. In that case, Proc Mi & Proc Mianalyse (SAS 9.4) will be used.

Multiple imputation inference involves three distinct phases:

1. The missing data are filled in *m* times to generate *m* complete data sets. (Proc Mi)
2. The *m* complete data sets are analyzed using standard statistical analyses. (Proc Mi)
3. The results from the *m* complete data sets are combined to produce inferential results (Proc Mianalyse).

8. CHARACTERISTICS OF STATISTICAL ANALYSES:

Descriptive statistics for continuous variables will be presented with *N, Mean, SD (standard deviation), Median, Q1-Q3 (first and third quartile),* where *N* denotes the number of subjects contributing with non-missing data.

For discrete variables, descriptive statistics will be presented with *N* and *percentage* of the number of subjects contributing with non-missing data in the various categories of the variable; the number of missing data will be presented but will not be taken into account in the percentage.

All statistical tests will be carried out as two-sided on a 5% level of significance. All confidence intervals will be 95% intervals.

Comparison between pre and post-operative endpoints for paired proportions will be done by a Mc Nemar's test for binary variables.

Comparison between pre and post-operative endpoints for continuous variables will be done by a paired t-test if they are normally distributed. In case of absence of normality, the alternative is to use Wilcoxon's signed-rank test.

For both continuous or binary variables, the null hypothesis is "no difference between pre and post implantation" against the general alternative of "difference between pre and post implantation".

<u>For effectiveness analyses:</u>

In order to present a smoothing scatter plot of these parameters' evolution over time, a non-parametric technique called LOESS will be used: LOESS is a type of local polynomial regression and is a generalization of moving average and polynomial regression; LOESS fits a localized regression function to data with a chosen neighborhood of points. At each point of the dataset, a low degree polynomial (linear or quadratic) is fitted to a subset of the data, with explanatory variables values near the point, whose response is being estimated: the polynomial is fitted using weighted least squares, giving more weight to points near the point whose response is being estimated and less weight to points further away. The value of the regression function is then obtained by evaluating the local polynomial using the

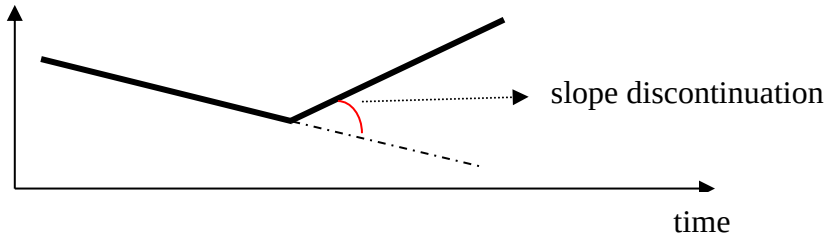
explanatory variables value which are in the local neighbourhood for that data point. The LOESS fit is complete after regression function values have been computed for each of the data points.

Furthermore, these repeated data are inherently unbalanced because patients did not come to all planned visits (missing data) and because the time between 2 consecutive visits is not always the same.

Consequently, specific longitudinal models must be used to take into account these unbalanced data. Mixed models containing fixed effects and random effects (intercept and/or slope) must be used and specific covariance structure to model within subject variation (R matrix) must be choosen.

If the smoothing scatter plot suggests trends with slope discontinuation over time, a mixed piecewise linear model including knots will be used.

The following pattern illustrates such piecewise linear models.



<u>For safety analysis:</u>

Incidence rates will be calculated by using: IR= number events/number of person-years.

Confidence interval will be calculated with an exact method based on the Poisson distribution. Complication free survival will be estimated by using the Kaplan-Meier method. If event date is lacking, we will impute by the middle date between visit concerned and the previous one. The distribution of mean of cumulated events over time, taking into account that multiple events per patient may occur, will also be presented, globally and stratified by the main 'high level terms'.

Standardized incidence rate may also be calculated (if data are available) in order to compare the number of side effects observed really in the Altis SU17 study, to the number expected if incidence rates stratified in year-classes and presence or no of prolapse, were the same as in general population. A SIR of 100 indicates that the number observed is equal to number expected, a SIR lower than 100 indicates than the number observed is lower than the number expected, a SIR greater than 100 indicates than the number observed is higher than the number expected. Testing if SIR is equal to 100 will be done.

A. Factors associated with treatment success:

Factors associated with treatment success will be assessed through logistic regression:

Univariate models will be performed with all variables suspected or known to be linked with treatment success such as age, BMI, SUI vs MUI, Pelvic Organ Prolapse, cause of stress component, active lifestyle, smoker, diabetes mellitus, recurrent UTI, severity of urinary incontinence (number of pads /day), Chronic bronchitis/cough (COPD), surgical incontinence treatment (bulking agents, sling, burch…), previous conservative treatments (pelvic floor exercise, biofeedback, bladder training, electrical vaginal stimulation), previous treatment by medication (oestrogen), post menopause, neurological disorders, PVR > 100 ml, preexisting dyspareunia, hysterectomy, relevant non obstetrical/gynecological surgery or medical history and other relevant disease.

1) For continuous variables, different cut-off will be used and the optimal threshold will be chosen by comparing AIC.

2) Only variables associated with $p < 0.20$ in the univariate models will be selected for the multivariate models. Backward, forward or stepwise effect selection methods will be used.

B. **Factors associated with complications:** voiding symptoms and non-urogenital pain:

Factors associated with first occurrence of voiding symptoms or non-urogenital pain will be assessed through survival analysis (Cox model):

1) Univariate models will be performed with all variables suspected or known to be linked with voiding symptoms or non-urogenital pain such as:
    - For voiding symptoms: age, POP repair (medical history), POP repair (concomitant surgery), neurological disease/condition, abnormal bladder capacity (>500 ml), abnormal PVR (>50mL), abnormal PVR (>100mL), concomitant medication, obesity, menopause, Pelvic floor muscles training/exercises…
    - For non-urogenital pain: age, lifestyle, hysterectomy, POP repair (medical history), concomitant pelvic surgery, Altis surgery duration …

   For continuous variables, different cut-off will be used and the optimal threshold will be chosen by comparing AIC.

2) Only variables associated with $p < 0.20$ in the univariate models will be selected for the multivariate models. Backward, forward or stepwise effect selection methods will be used.

9. PLANNED STATISTICAL ANALYSES:

The number of each visit (baseline, operative, immediate post-operative follow-up, first follow-up visit, 1 year, 2 years, 3 years) completed will be described as well as the distribution of the latest follow up visit completed. The number and repartition by visit of self-questionnaires will be provided.

9.1 Descriptive Analysis (patients, procedure, study exit):

The first tables will describe the patients before the procedure:

A. DESCRIPTION BEFORE INTERVENTION

a. Demographic information, urogynecological and medical history

- General (age, BMI)
- Diagnostic (SUI, MUI)
- Cause of stress component (HU, ISD)
- Previous incontinence treatments
- Previous surgical incontinence treatments
- Lifestyle (activity, smoker)
- Coexisting diseases
- Obstetrical/gynecological history
- Relevant not obstetrical/gynecological surgery or medical history
- History and general symptoms assessment during baseline
- Number of pads used

b. Physical examination / interview patient

- Result of cough stress test
- Cervico-urethral mobility
    - Marshall/Bonney Test (sub cervical support maneuver) positive
    - Ulmsten Test (sub urethral support maneuver)
    - Q Tip/cotton swab Test:
- Presence of Pelvic Organ Prolapse: localization, grade

c. Investigations

- Pad Weight testing
- Post void residual volume (PVR)
- Maximum flow rate (Q max.)

d. Urodynamic testing

- Cystometry
- Urethral pressure measurement

e. Results of patient questionnaires before intervention

- Demographic questionnaire
- ICIQ- UI SF
- PISQ-12
- I-QOL: total and subscores

B. PROCEDURE DESCRIPTION

- Pre-operative and intraoperative antibiotics
- Anesthesia
- Duration
- Blood loss
- Concomitant pelvic surgery
- Technical observations during procedure

C. DESCRIPTION IMMEDIATE POSTOPERATIVE FOLLOW-UP

- Post-operative antibiotic
- Normal urination
- Bladder drainage
- Local pain
- Postoperative stay/duration
- Post void residual volume (PVR)
- Maximum flow rate (Q max.)

D. STUDY EXIT /WITHDRAWAL

- Completion of the study as planned
- Primary reason in case of discontinuation.

9.2 Effectiveness Analysis:

I. Primary endpoint **at one year**:

- PGI as a little, much better and very better improved and absence of neither severe or serious related Adverse Event classification (as protocol).
- PGI as much better and very better improved, and absence of neither serious or severe or ≥ Grade 3 Clavien-Dindo related Adverse Event (as SC recommendations)

II. Secondary endpoints:

- PGI as a little, much better and very better improved and absence of any severe neither serious related Adverse Event at first follow-up visit, 2 years and 3 years after implantation (as protocol).
- PGI as much better and very better improved and absence of neither severe or serious or ≥ Grade 3 Clavien-Dindo classification related Adverse Event at first follow-up visit, 2 years and 3 years after implantation (as SC).
- PGI as much better and very better improved and absence of serious related Adverse Event at first follow-up visit, 1 year, 2 years and 3 years after implantation (as SC).
- PGI as much better and very better improved and absence of ≥ Grade 3 Clavien-Dindo classification related Adverse Event at first follow-up visit, 1 year, 2 years and 3 years after implantation (as SC).
- PGI as a little, much better and very better improved at first follow-up visit, 1 year, 2 years and 3 years after implantation (as protocol).
- PGI as much better and very better improved at first follow-up visit, 1 year, 2 years and 3 years after implantation (as SC).
- Satisfaction at first postoperative visit, 1 year, 2 years and 3 years after implantation.
- Recommendation to a friend at first follow-up visit at 1 year, 2 years and 3 years after implantation.

Evolution over time of continuous outcomes (post-void residual volume, maximum flow rate, pad weight test, number of pads/day, total I-QOL score and subscores, total PISQ-12 score, total ICIQ SF score) or binary variables (cough stress test) will be presented.

The result of these outcomes will be presented for baseline, first operative visit, 1 year, 2 years and 3 years after implantation. Differences with the baseline will be presented and particularly for the questionnaires, where absolute and relative differences of the different scores will be calculated. Evolution will be graphically presented and a smoothing scatter plot of the different parameters over time by using a non-parametric technique (LOESS).

For the self-questionnaires (IQOL, PISQ-12, ICIQ), the cough stress test and number of pads/day: 5 measures are theoretically available by patient (baseline, first follow-up visit, 1 year, 2 years and 3 years), whereas only 3 measures are available by patient for post-void residual volume and peak urine flow rate…
Effect of time will also be tested by a mixed linear model (SAS Proc Mixed) or GEE model (SAS proc genmod). If needed, an extension of mixed model or GEE model such as piecewise linear models will be used to model a potential slope discontinuation over time.
If too many missing data, the alternative is to compare value at 3 years with value at baseline by a Wilcoxon‘s signed-rank test (continuous variables) or Mc Nemar’s test (binary variables).

9.3 Safety endpoints:

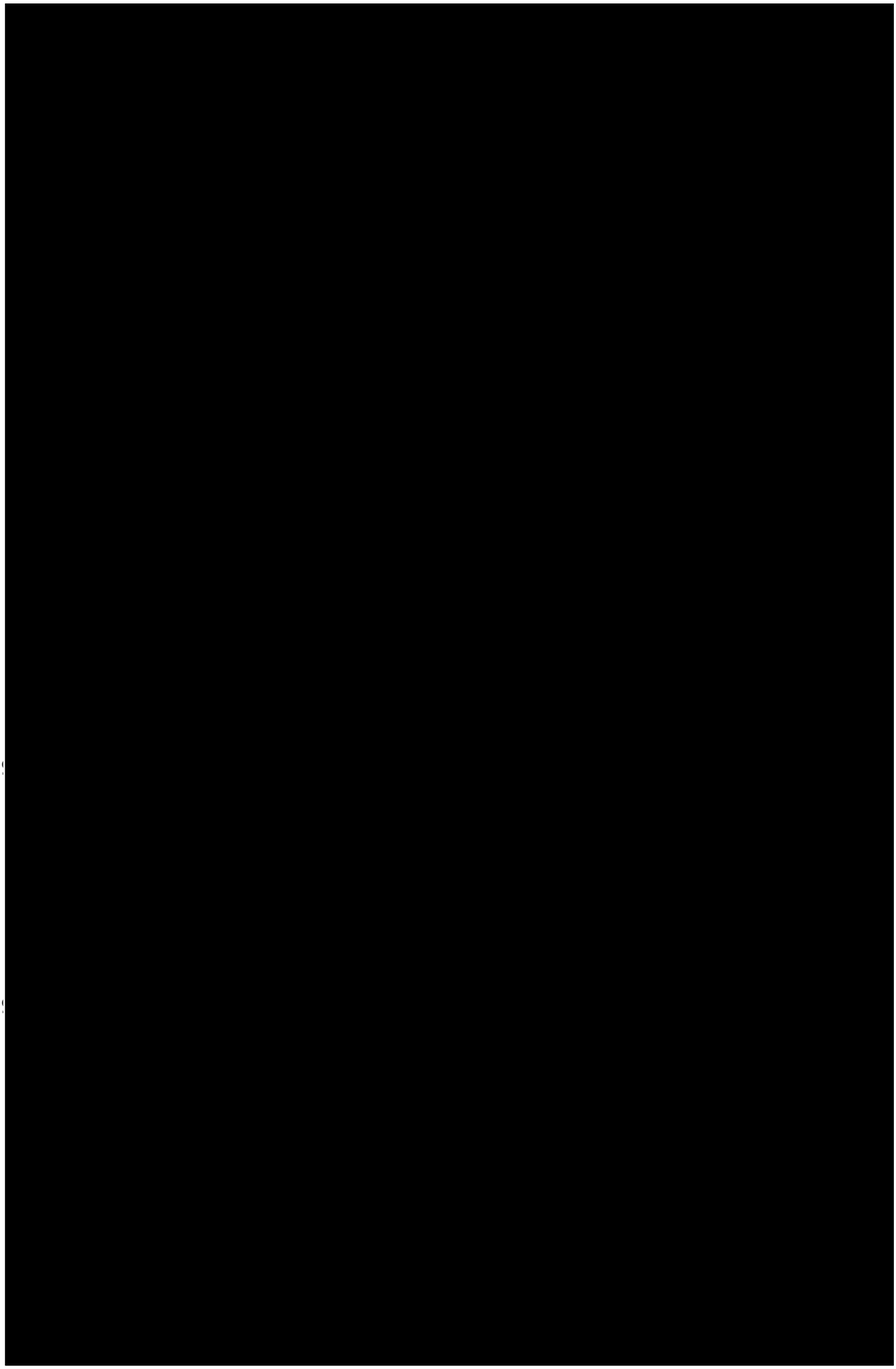
A review by a Safety Committee will take place in order to classify the events declared into side effects events, technical observations and post-operative observations. This committee will also adjudicate on the relatedness of events (procedure or device), their seriousness, preferred term and classify them according the Clavien-Dindo classification).
The Safety Data Committee will adjudicate on the events reported by patients in the patient’s questionnaires and not confirmed as related by the investigator.
The Clavien-Dindo is widely used throughout surgery for grading events (complications) which occur as a result of surgical procedures, grading complications by the extent of therapy necessary to resolve them.
The adjudication by the Safety Committee will be considered as the final decision.

Tables will present the following data concerning side effects occurred since implantation: type, severity, intensity, relatedness (device/procedure), Clavien-Dindo classification, Side-Effect

(=Preferred Terms when possible), SOC and High Level Term according to MedDRA, sling revisions (and description), treatments given and localization (if pain), according to time of clinically diagnosed (intraoperative vs postoperative and IUGA Time division from T1 to T4).

Incidence rates with 95% confidence interval will be calculated between operative procedure and the last follow-up visit available with an exact method based on the Poisson distribution on 'SOC' and 'High Level' terms (MedDRA classification), except for 'High Level'= pain which will be divided into 2 possible Side-Effects: 'Non urogenital pain' or 'Urogenital pain'.
The distribution of mean of cumulated events over time, taking into account that multiple events per patient may occur, will also be presented globally or stratified by the main 'High Level Term' ('Bladder storage symptoms', 'exposure and extrusion', 'Urinary Tract Infection', 'Voiding symptoms', 'pain' itself divided into 'Non urogenital pain' or 'Urogenital pain').

[redacted]



10. SOFTWARE:

All statistical analysis and programming will be done using the SAS software version 14.3.